Pharmacology Biochemistry & Behavior, Vol. 23, pp. 995–1002, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

The Effects of Acute and Repeated Clonidine Administration on Fixed-Interval Performance in Rhesus Monkeys[1]

WILLIAM D. WESSINGER[2] AND ROBERT L. BALSTER[3]

Department of Pharmacology and Toxicology Medical College of Virginia Virginia Commonwealth University, Richmond, VA 23298

Received 5 November 1984

WESSINGER, W. D. AND R. L. BALSTER. *The effects of acute and repeated clonidine administration on fixed-interval performance in rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **23**(6) 995–1002, 1985.—The effects of clonidine before, during and after 95 days of chronic administration of 100 μg/kg/day clonidine were investigated in five rhesus monkeys which had been trained to lever press under a fixed interval 5-min schedule of food presentation. The effects of clonidine (3–100 μg/kg) were generally to cause dose-related decreases in rates of responding and quarter-life, and increases in the line slopes of rate-dependency plots. Before chronic treatment, 200 μg/kg of clonidine caused somewhat less response rate suppression than 100 μg/kg. During chronic treatment, one monkey showed some development of tolerance to the rate-suppressant effects and another showed tolerance to the quarter-life effects, but the group as a whole did not show evidence of tolerance development to these effects of clonidine. Following cessation of chronic treatment, no overt signs of dependence were observed, however, some subjects did show disruption of schedule-controlled performance during the first week. In general, however, no consistent evidence for the development of tolerance or dependence to clonidine were observed under these dosing conditions.

Clonidine Rhesus monkeys Fixed-interval schedule Tolerance Dependence Rate dependency

CLONIDINE (2-(2,6-dichlorophenylamino)-2-imidazoline) was synthesized by Stähle in 1962. Like other imidazolines, it has a broad spectrum of pharmacological actions. It was originally developed as a nasal decongestant, but its antihypertensive actions soon became evident and it was marketed in 1966 for this purpose [12]. More recently, clonidine has been used as an agent to suppress or eliminate withdrawal symptomology in opiate addicts [9, 28, 29], and thus its acute and chronic behavioral effects have become of interest.

Clonidine has been shown to share several properties with opiates including the development of tolerance to its effects. It produces antinociception in laboratory animals [6, 19, 22, 24] and tolerance to this effect as well as cross-tolerance to morphine has been demonstrated [20]. Tolerance occurs to the effect of clonidine on operant responding in rats, and upon discontinuation of repeated administration, a withdrawal syndrome similar to opiate withdrawal has been observed [17]. Rhesus monkeys self-administering IV injections of clonidine under unlimited access conditions exhibited tolerance to the observed ptosis and sedative effects of the drug, and at 10 μg/kg/injection were able to self-administer high doses averaging 3.6 mg/kg/day [30]. In order to further characterize the behavioral actions of clonidine and to quantify the development of tolerance, the effects of acute and chronic administration of clonidine on responding under a fixed-interval (FI) schedule in rhesus monkeys were evaluated. A decreased effect of clonidine with chronic daily administration and/or a shift of the dose-effect curve for clonidine to the right, following repeated clonidine exposure, would be considered evidence for the development of tolerance.

METHOD

Animals

The subjects were five adult male rhesus monkeys (*Macaca mulatta*) that weighed between 7.2 and 10.6 kg at the beginning of the experiment. Four of the animals (B002, B4115, 4156 and M324) had a history of FI responding following acute administration of drugs, but at least three drug-free months intervened between studies. The fifth monkey (M325) was naive to both behavioral procedures and drugs. They were maintained at a constant weight throughout the study be adjusted post-session feedings (Purina Monkey Chow), except M325 who was reduced to 90% free-feeding weight during initial training, then gradually returned to his original weight. The animals were individually housed in an

[1]Research supported by the National Institute on Drug Abuse (NIDA) contract 271-81-3830. A portion of this research was reported at the annual meeting of the American Society for Pharmacology and Experimantal Therapeutics, August 15–19, 1982, Louisville, KY, USA.

[2]Predoctoral Fellow supported by NIDA training grant DA-07027. Present address: Department of Pharmacology and Interdisciplinary Toxicology, University of Arkansas for Medical Sciences, 4301 West Markham, Mail Slot 638, Little Rock, AR 72205.

[3]Requests for reprints should be addressed to R. L. Balster.

isolated room in standard primate cages (0.6×0.7×0.8 m). Food was supplemented daily with a chewable multivitamin tablet and weekly with fruit. Water was freely available in the home cages, but not during experimental sessions.

Apparatus

Experimental sessions were conducted in a separate room in a converted upright refrigerator shell equipped with a ventilation fan which also served to mask room noises. During experimental sessions the monkeys were seated in a primate chair and restrained by a waist stock and shoulder rings. When placed in the chamber, the monkeys faced the door upon which were mounted a response lever with three stimulus lights above it, and a food trough. Responses on the lever resulted in the delivery of two 1-g food pellets (Formula L, P. J. Noyes, Co., Lancaster, NH) by an automatic pellet dispenser (BRS/LVE, Beltsville, MD) mounted outside on the door. Experimental contingencies were controlled by solid-state programming equipment located in an adjacent room. Data were recorded automatically as response totals for each successive minute of the fixed intervals, cumulative over the session, and as cumulative response recordings.

Procedures

Animals were trained to seat themselves in the primate chair for transport from the home cage area to the experimental chamber. Four of the animals had already been trained to respond under a multiple FI 5-min time-out 1-min schedule of food presentation. At the beginning of the session, the stimulus lights were lit and the first lever press after 5 min resulted in food presentation. If an animal failed to respond within 1 min after the 5-min FI had elapsed (limited hold 1 min) the available food pellets were forfeited and the schedule advanced to the 1-min timeout, during which the lights were extinguished and responses had no consequences. The session terminated after the tenth timeout component resulting in session durations of between 60 and 70 min. Sessions were usually conducted 5 days per week, Monday through Friday.

The naive animal, M325, was trained as the others had been previously, to seat himself in the primate chair for transport to the experimental area. Following adaption to this procedure and mild food deprivation he was placed into the chamber and trained to respond on the lever on a fixed-ratio 1 schedule (FR-1) by successive approximation. After initiation of responding for food on an FR-1, the ratio was advanced stepwise to an FR-10. At this point, the schedule was changed to an FI-10 sec with no limited hold and no time-out and the interval length was advanced gradually to the final 5-min schedule (FI-5). Finally, the 1-min time-out component and 1-min limited hold contingency were added. Training continued until the quarter-life was consistently above 0.5 and the cumulative response records revealed the characteristic positively-accelerated pattern usually seen in FI responding [5].

Training for all the subjects continued until the baseline rate of responding was stable. The criteria for stability was when overall response rates for three consecutive sessions varied by less than 20%. Following training, the experiment proceeded in three phases.

Phase 1, Determination of Acute Drug Effects

In Phase 1 the acute effects of doses of clonidine and vehicle (saline) were examined. The doses used were 3, 10, 30, 100 and 200 μg/kg and were administered twice in each subject in a counterbalanced sequence except that the high dose was administered last. Three days of stable overall response rates were required before each dose was administered, thus drugs were administered no more often than twice a week. Clonidine or vehicle was administered IM just prior to the beginning of the session.

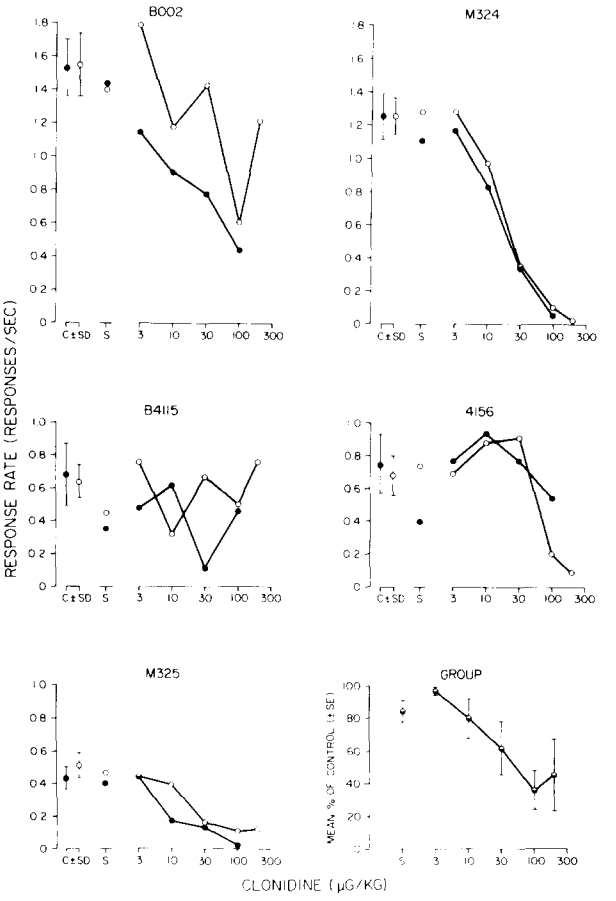

FIG. 1. The effects of saline vehicle (S) and IM clonidine on the overall rates of responding under a FI 5-min schedule of food presentation are shown for five rhesus monkeys as well as for the group. Except for the highest dose (200 μg/kg), each dose was tested twice; closed points (●) were the results from the first dose-effect series, open points (○) from the second series. Control data (C) is the mean rate of responding (±SD) for the three sessions that preceeded the doses of clonidine or vehicle tested during each determination. The lower right hand panel shows the combined data for the group. Drug and vehicle effects have been expressed as a percentage of the control values (▬) and averaged for the five monkeys (±SE).

Phase 2, Chronic Drug Administration

Following the determination of the acute dose-effect curves, the subjects received 100 μg/kg clonidine daily, seven days a week, for 95 consecutive days. This dose was chosen on the basis of the acute effects as a dose which caused marked, but not complete, suppression of response rates for the group. Operant sessions occurred immediately following drug administration five days a week. During the last three weeks of the chronic phase, test sessions were

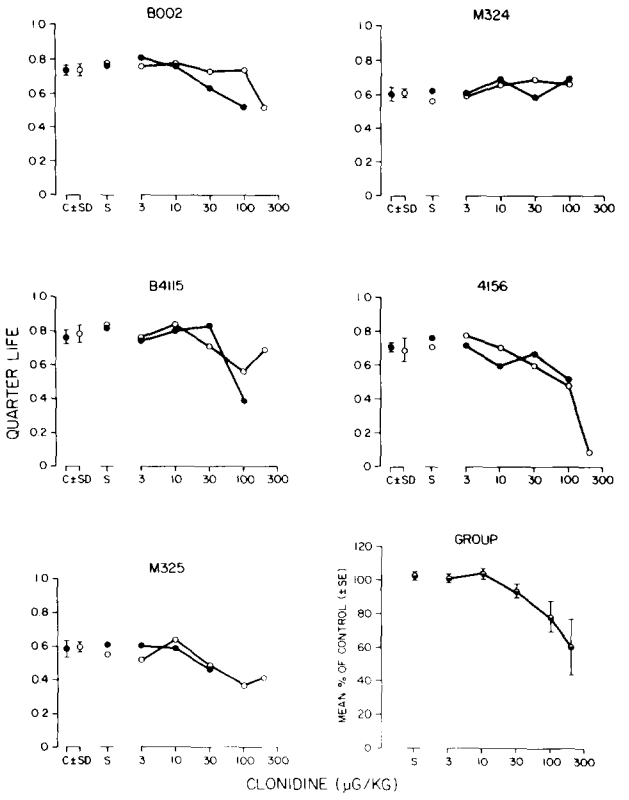

FIG. 2. The effects of saline vehicle (S) and IM clonidine on the pattern of FI responding as measured by quarter-life are shown for five rhesus monkeys as well as for the group. Quarter-life is that proportion of the FI which elapsed by the time 25% of the total responses were emitted. Except for the highest dose (200 μg/kg), each dose was tested twice; closed points (●) were the results from the first dose-effect series, open points (○) from the second series. Points where the overall response rate was less than 0.05 responses/sec have been omitted and are not included in the group data. Control data (C) is the mean quarter-life (±SD) for the three sessions that preceeded the dose of clonidine or vehicle tested during each determination. The lower right hand panel shows the combined data for the group. Drug and vehicle effects have been expressed as a percentage of the control values (●) and averaged for the five monkeys (±SE).

conducted on Tuesdays and Fridays using doses of clonidine (3, 10, 30, 100 μg/kg) or saline administered just prior to the session and the balance of the 100 μg/kg/day dose administered just after the session to determine the dose-effect curve for clonidine during Phase 2. Data was collected in the same manner as before.

Phase 3, Redetermination of Acute Effects Following Chronic Treatment

In Phase 3 chronic administration of clonidine was discontinued and the operant sessions were conducted for seven days without injections. Then, as soon as the stability criteria was met, dose-effect curves were determined once as in Phase 1.

Drugs

Clonidine hydrochloride (provided by A. E. Jacobson, National Institute of Health) was dissolved in physiological saline to the appropriate concentration to give an injection volume of less than 1.0 ml. Physiological saline was used as the vehicle control and was injected in a volume of 0.1 ml/kg. Doses are expressed as μg/kg and are calculated on the basis of the salt. Injections were given IM into the thigh muscle.

TABLE 1

AVERAGE SLOPE OF RATE-DEPENDENCY LINES AS A FUNCTION OF CLONIDINE DOSE

	Vehicle or Clonidine (μg/kg)					
	Saline	3	10	30	100	200
Average slope*	0.09	0.05	0.03	−0.25	−0.64	−0.54
S.E.	0.06	0.07	0.09	0.09	0.08	0.13
N	10	10	10	10	9	4

*Values are the averages of two determinations in five subjects except for the 200 μg/kg dose where only one determination was made. Slopes were not included in the average when the overall response rates were less than 0.05 responses/sec.

Data Analyses

Overall rates of responding during the FI component for baseline sessions and sessions that were preceeded by clonidine or vehicle injections were calculated and individual and group means and SE's are presented. For rate-dependency analysis [14], the FI was divided into five 1-min segments and the drug effects on the local response rates for each segment were plotted as a percentage of the control rates on a logrithmic scaled ordinate versus the response rate for the corresponding segment during control conditions on a logrithmic scaled abscissa. Control conditions were defined as the overall average rate of responding for the three days preceeding injections of drug or saline during each dose-effect determination. Control rates and drug rates were determined for individual animals. In addition, the slopes of the lines from rate-dependency analysis (linear regression of logrithmic transformed data) are presented as the average of the individual determinations. The cumulative responses collected separately for each 1-min segment of the FI's were used to calculate quarter-life by linear interpolation as the proportion of the interval elapsed before one-quarter of the total responses in the interval were made.

RESULTS

Phase 1, Acute Effects

The initial effect of clonidine on responding under the FI schedule was generally to decrease response rates in a dose-related manner with effects seen at doses as low as 10 μg/kg (Fig. 1). However, in one monkey (B4115) this was not the case. This monkey exhibited rather large vehicle effects and drug effects were inconsistent (note the different response to 30 μg/kg in the first and second determination). Overall response rate decreases were generally not seen in this monkey. In three of the five monkeys the response rate was greater at 200 μg/kg than at 100 μg/kg, possibly indicating a non-linear dose-effect function as seen in the group curve. Higher doses than 200 μg/kg were not tested because of severe bradycardia that resulted from this dose. In four mon-

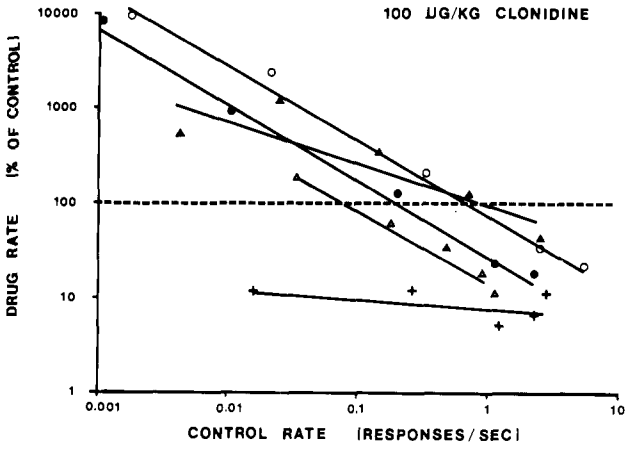

FIG. 3. Rate-dependent effects of 100 μg/kg clonidine in individual animals. The change in response rates after drug administration is plotted as a function of mean pre-drug control rates during each successive min of the FI. Individual symbols and lines represent the results in different monkeys where ○=B002; ●=4156; △=M325; ▲=B4115; +=M324.

keys which would tolerate use of a stethoscope, an informal assessment of heart rate was conducted. The normal rate was determined to be 146–160 BPM. Following the session where 200 μg/kg of clonidine was administered, heart rate was reduced to 46–60 BPM.

The effect of clonidine on the pattern of responding, as measured by quarter-life, was also generally to produce dose related decreases (Fig. 2). However, as with response rate, there were individual differences and the effect on quarter-life did not always correlate well with response rate effects. For example, monkey M324 had orderly dose-dependent effects of clonidine on response rates (Fig. 1), yet there were no effects of clonidine on quarter-life. On the other hand, the effects of clonidine on quarter-life for B4115 was relatively dose related yet overall response rates for this monkey were not reliably affected by increasing doses of clonidine. Both these cases are in contrast to what is seen in monkeys 4156, M325 and to some extent B002 where dose-effect relationships on response rate are closely paralleled by quarter-life decrements with increasing doses. Again, as seen with the effects of clonidine on response rates, 200 μg/kg caused an increase in quarter-life over that seen following the 100 μg/kg dose in two (B4115, M325) of the five monkeys, although for this measure the average for the group was monotonic decreases in quarter-life.

Table 1 shows that the slopes of the lines in the rate-dependency analyses became more negative with increasing doses up to 100 μg/kg. Figure 3 shows the rate-dependency plots for the second determination of 100 μg/kg clonidine in each subject to illustrate individual differences in these effects. Those monkeys which showed dose-related decreases in response rate and quarter-life (B002, 4156, M325) also revealed rate-dependent effects. The exceptions were B4115 which showed clear rate-dependent effects which were not accompanied by consistent response-rate changes and M324 who had clear dose-related response rate decreases which were not accompanied by linear dose-related rate-dependency plots.

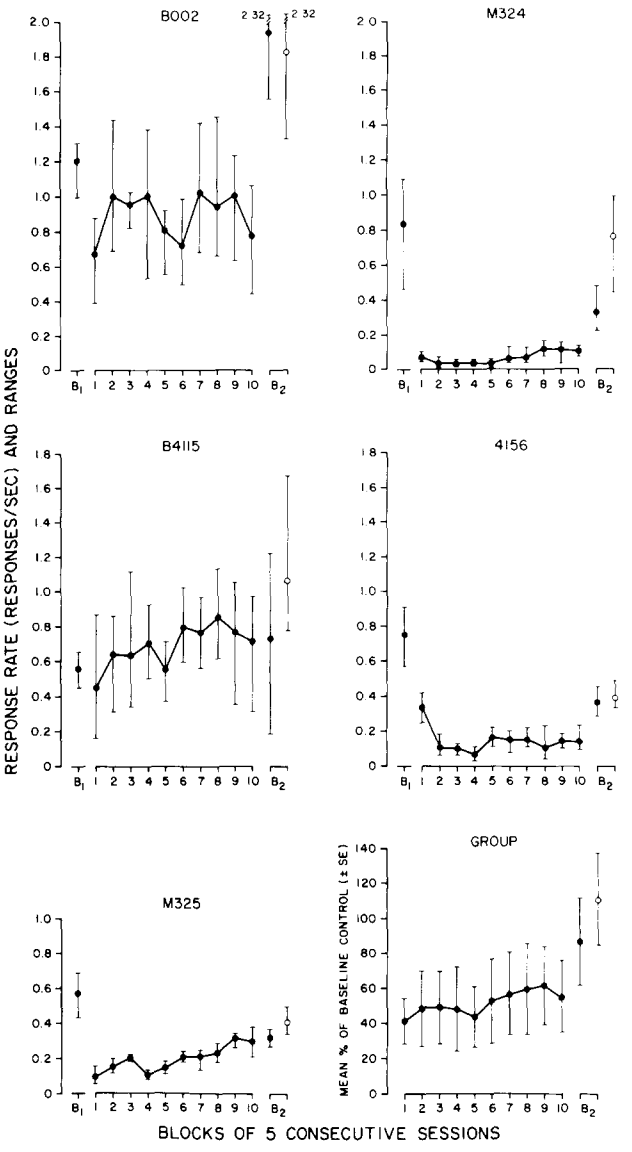

FIG. 4. Effects of daily injections of 100 μg/kg clonidine on overall response rates for five rhesus monkeys as well as for the group. Average response rate (±range) for the five non-drug days preceeding chronic treatment (B1), for successive 5-day segments of the chronic treatment phase, for the first five non-drug days following chronic treatment (closed points, B2) and the last five non-drug days preceeding redetermination of the dose effect curves after chronic treatment (open points, B2) are shown. The lower right hand panel shows the combined data for the group where response rates have been expressed as a percentage of the prechronic control values (B1) and averaged for the five monkeys (±SE).

Phase 2, Chronic Effects

Figure 4 shows the average baseline response rates and ranges for the five non-drug days preceeding chronic administration of 100 μg/kg clonidine (B1) and the average response rate and ranges for ten successive five-day segments during the chronic phase where 100 μg/kg clonidine was administered just prior to each session. In four of the five monkeys (B002, M324, 4156 and M325) the response rates were suppressed compared to baseline (B1) for the duration

of repeated clonidine administration with only M325 showing some return toward baseline rates of responding. As was the case during initial testing of acute effects, monkey B4115 was not reliably affected by 100 μg/kg throughout the chronic regimen, although on the first three days decreases to about 30% of control levels were observed, and an increased variability was seen throughout treatment with this dose. When the average response rates for the individual animals were converted to the percentages of their baseline rates (B1) and averaged for the group, the mean response rates were suppressed to 40 to 60% of control during Phase 2 (lower right panel, Fig. 4) with little evidence for substantial recovery. Similarly, quarter-life values were suppressed initially for all subjects (50 to 85% of baseline) and remained so over the chronic treatment phase, except for monkey M324 (data not shown). Although his response rate did not return to control (Fig. 4), quarter-life returned toward baseline over repeated administration.

The effects of the various doses of clonidine and saline on response rates, assessed towards the end of repeated administration are shown in Fig. 5 (solid squares). There was little evidence for a consistent change in sensitivity to the acute effects of clonidine compared to its initial effects (shaded area). The response rates determined during repeated dosing were generally dose related and within or close to the original ranges for monkeys B002, 4156 and M325. For M324 the response rate for saline and the four doses of clonidine tested remained low over the entire dose range, and comparable to response rates on the days this subject received his usual 100 μg/kg dose of clonidine (cf. Fig. 4). In contrast, B4115 (who originally showed inconsistent dose-related effects) had response rates greater than the original range for the three lower doses of clonidine (3, 10, 30 μg/kg). The effect of 100 μg/kg for M325 (who showed some development of tolerance over the period of chronic dosing) was much higher than originally determined, close to the range of the original saline and control response rates (81% of original control rate).

The effects of saline and doses of clonidine tested during repeated administration were converted to a percentage of each individual subject's initial control rates and averaged for the group (lower right panel, Fig. 5). The effects of saline and doses of clonidine determined during repeated administration for the group are close to or within the range of two standard errors from the mean of the original effects.

Phase 3, Postchronic Effects

None of the monkeys showed any overt physical signs of withdrawal during the week following cessation of chronic dosing. The solid points over B2 in Fig. 4 show the average response rates for the first five non-drug days following cessation of chronic treatment and the open points represent the average response rates for the last five non-drug days preceeding the redetermination of acute effects of clonidine. The return to baseline levels was quite variable from subject to subject. One subject (B002) initially showed a large increase in response rate to greater than 2.0 responses/sec which gradually declined to prechronic levels; another (B4115) initially exhibited very low rates (0.2 responses/sec) which increased steadily over seven daily sessions to much greater than prechronic levels (1.9 responses/sec) before leveling off; M324 and M325 gradually returned to baseline levels during the first week while response rates for 4156 remained at about half of the prechronic rate (0.35 responses/sec) for the remainder of the experiment—never returning

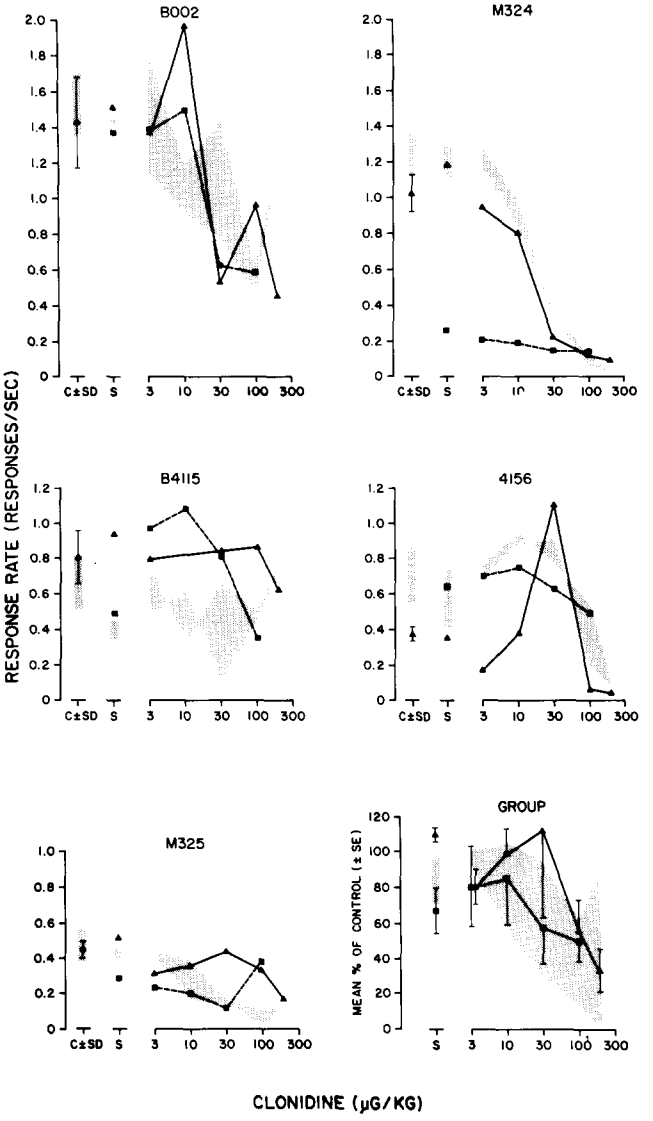

FIG. 5. The effects of saline vehicle (S) and IM clonidine on overall rates of responding determined during the chronic treatment phase and after cessation of chronic treatment compared to the initial acute effects. Panels show results in five rhesus monkeys as well as combined data for the group. For the individual subject panels, control data (C) is the mean rate of responding for the three sessions that preceeded each dose of clonidine or vehicle tested. The shaded areas over C are the overall mean control response rates (±S.D.) for the prechronic phase determinations and the solid triangles (▲) over C are the postchronic mean control response rates (±S.D.). Shaded portions over S (saline) and doses of clonidine are the ranges of response rates for the first and second prechronic determinations. Solid squares (■) are the effects of saline vehicle (S) and doses of clonidine tested during the chronic treatment phase of the experiment. Solid triangles (▲) are the effects of saline and clonidine after the chronic treatment phase of the experiment. The lower right hand panel shows the combined data for the group. The effects of saline vehicle and doses of clonidine for the three phases (prechronic, chronic, and postchronic) of the experiment were expressed as a percentage of the prechronic control values and averaged for the five monkeys. Shaded portions are the prechronic effects of saline (S) and doses of clonidine (±2 S.E.'s). Solid squares (■) are the effects determined during the chronic phase (±S.E.) and solid triangles (▲) are the effects determined after the chronic phase of the experiment (±S.E.).

to prechronic baseline levels. Thus, the group data (lower right panel, Fig. 4) shows that recovery of baseline rates of responding occurred.

In general, quarter-life values (data not shown) returned to prechronic baseline levels the session following cessation of chronic treatment except for M324 whose quarter-life values had already returned to prechronic control levels during repeated administration.

Dose-effect determinations for saline and doses of clonidine following chronic treatment again yielded variable results between subjects (Fig. 5, solid triangles). Control response rates during this phase were within or close to the original values of prechronic rates for B002, M324, B4115 and M325. Control response rates for 4156 remained at about 50% of initial levels. Responding after saline injections also returned to close to initial ranges except in the case of B4115 (whose original saline response rates were rather suppressed compared to control levels), where the new saline response rates were now at about control level. The effects of doses of clonidine were generally linearly dose-related for B002 and M324, as they were originally. Monkey B4115 remained insensitive to the rate-suppressing effects of clonidine and M325 did not show suppression until the highest dose. The dose-effect function for 4156 remained as an inverted U-shaped function as before, except that 3 and 10 μg/kg clonidine had more marked rate suppressant effects. When response rates were expressed as a percentage of the individuals' average control rates for Phase 3 and averaged across the group, the dose-effect function remained within the normal range (± 2 SE) (lower right panel, Fig. 5). Saline response rates for the group were elevated due to the contribution of B4115's increased saline response rate.

DISCUSSION

The acute effects of clonidine were generally to cause dose-dependent decreases in FI response rates in rhesus monkeys. This is in agreement with other published reports of the effects of clonidine on schedule-controlled responding including FI schedules in rats [8, 10, 11], FR schedules in rats [2, 4, 11, 16, 23] and mice [13], differential reinforcement of low rate (DRL) schedules in rats [27], and complex schedules in pigeons (multiple FI-FI, [13]) and rats (tandem VI-FR, [3]). The clonidine doses that suppressed FI response rates in the present study using primates were similar to the effective doses in suppressing FI response rates in studies using rodents and pigeons. There was considerable individual variability in the effects of clonidine in primates on response rate, and one subject (B4115) did not show reliable effects on overall response rates. However, this subject did show effects in response patterning as measured by quarter-life and rate-dependency analysis.

The acute effects of clonidine on response patterning was generally to cause a dose-related decrease in quarter-life, however, as with the acute effects of clonidine on response rate, there was considerable variability between subjects. One subject (M324) did not show effects of clonidine on quarter-life, yet clonidine had reliable response rate suppressant effects on this subject. The effects of clonidine were shown to be related to control rates of responding. Rate-dependency analysis revealed a linear relationship between the log of the effect and the log of the baseline rates during different portions of the interval. Harris *et al.* [11] reported rate-dependency data for the effects of clonidine on FI responding in rats with similar results. Like the findings reported here, these rate-dependent effects increased with dose, that is, the slopes of the rate-dependency lines became increasingly negative with increasing doses of clonidine. This evidence for log-linear rate-dependent effects of clonidine demonstrate that subtle behavioral effects similar to those produced by standard psychoactive drugs [14] can be produced by clonidine.

Previous findings concerning the development of tolerance to the effects of clonidine have been contradictory. For example, some authors have reported that tolerance does not develop to the hypotensive effects of chronic clonidine [25,26] whereas others have reported development of varying degress of tolerance to this effect [1,15]. Tolerance to the antinociceptive actions of clonidine in rats and mice using the tail-withdrawal and tail-flick assays was not observed by Fielding *et al.* [7] and cross-tolerance to morphine in mice also was not observed [24]. These studies are in contrast to those of Paalzow [20] who used a vocalization threshold to electrical stimulation assay in rats to demonstrate both tolerance to clonidine's antinociceptive actions and cross-tolerance to morphine in rats given chronic clonidine. Tolerance to the behavioral effects of clonidine has also been reported. The exploratory behavior of rats in a Y-runway was initially suppressed by clonidine; but following seven days of exposure to clonidine via drinking fluids, tolerance developed to the extent that exploratory behavior was not different from controls [15]. Tolerance to the sedative effects in rhesus monkeys [30] and humans [18] has also been reported.

Tolerance to the response rate decreasing effects of clonidine on scheduled-control behavior was reported to develop in rats responding under a FR schedule following 14 days of chronic treatment via drinking water and daily injections [17]. After 35 days of chronic treatment, these rats showed disruption of operant responding for up to seven days following cessation of treatment. In contrast are the findings reported here on rhesus monkeys working on a FI schedule. During 95 consecutive days of chronic treatment with cloniding (100 μg/kg) the group showed no consistent evidence for the development of tolerance to the response rate decreasing effects of clonidine when compared to prechronic acute effects. However, one monkey (M325) did show some tolerance to the response-rate suppressant effects of clonidine during the chronic treatment phase, and when the dose-effect function was redetermined after chronic treatment, the response rate decreasing effects of 30, 100 and 200 μg/kg clonidine in this subject were less than the initially determined effects of these doses. On the other hand, quarter-life values for this subject did not improve during the chronic treatment phase. Another monkey (M324) showed development of tolerance to the quarter-life decreasing effects of 100 μg/kg clonidine during chronic treatment, but response rates remained severely depressing during the entire phase. Following chronic treatment, the dose-effect function for this subject was very close to the originally determined values. Despite these individual exceptions, the group data could not be used to support the finding of tolerance development.

Schuster *et al.* [21] have postulated that tolerance is more likely to occur to those drug effects that interfere with an animal's ability to obtain reinforcement. In this respect, the FR schedule as utilized by Meyer *et al.* [17] to demonstrate tolerance to clonidine's response rate decreasing effects would have been more condusive to the development of tolerance than the FI schedule used here. Response rate de-

crements in FR responding result in a loss in the number of reinforcers obtained, whereas only one response is necessary to obtain reinforcement on the FI schedule. Indeed, reinforcement rates during chronic clonidine in the present study were rarely below the maximum of ten reinforcements per session. In this context, the lack of consistent tolerance development in our study suggests that behavioral mechanisms may play an important role in tolerance to clonidine. Direct studies of the role of behavioral and pharmacological determinants of tolerance to the behavioral effects of clonidine in the same species using identical dosage regimens are needed to address this hypothesis.

It has previously been shown in rhesus monkeys that chronic intravenously self-administered clonidine led to physical dependence exhibited by withdrawal signs which included facial flushing, excessive scratching, refusal of preferred food, restlessness, salivation and emesis [30]. In the present study, none of the subjects exhibited overt signs of withdrawal following the cessation of chronic treatment. Large differences in daily dose of clonidine between the two studies could account for the difference. In the self-administration study subjects received daily doses averaging as high as 3.6 mg/kg/day, IV, compared to the 100 μg/kg/day, IM, doses in the present study. Also, in the earlier study, because access to clonidine was unlimited, injections occurred throughout the day. Multiple daily injections would be more likely to result in the development of dependence than single injections.

Some of the subjects showed disruption of schedule-controlled performance during the first week following cessation of chronic treatment which manifested itself in different ways. With the exception of 4156, the other subjects control response rates returned to about the prechronic level within 10 days of cessation of chronic treatment. In general, quarter-life values were at prechronic control levels the session following cessation of chronic treatment and did not show disruption. It should be remembered that these subjects had not responded at control rates for over 13 weeks, thus it may not be surprising, nor evidence of carry-over effects of clonidine or clonidine withdrawal, that recovery of initial baseline rates of responding required several days.

In conclusion, clonidine at doses as low as 10 μg/kg, IM, decreased response rate in rhesus monkeys responding under a FI-5 min schedule of food presentation. Effects on response patterning which were similar to those produced by many psychoactive drugs are evidence for subtle behavioral effects of clonidine. Repeated treatment with 100 μg/kg/day did not result in consistent tolerance development, although two of the five subjects showed some decrease in sensitivity to some of the effects.

ACKNOWLEDGEMENTS

The expert technical assistance of Earl E. Dowdy, Jr. and comments and suggestions of Dr. William L. Woolverton are gratefully acknowledged. We would also like to thank Bonny T. Hopkins and Brenda K. Selby for preparing the manuscript.

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